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FACSIMILE COVER SHEET

Atty. Dkt.: 7569/80993 **Date: October 19, 2004**

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Appl. No.: **10/811,793**
Filed: **March 19, 2004**
Title: **Treatment of Migraine Headache**
Inventor(s): **Plachetka, *et al.***
Atty. Dkt.: **7569/80993**

CERTIFICATE OF FACSIMILE

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:	
Plachetka, *et.al.*	Art Unit: 1616
Appl. No.: 10/811,793	Examiner: F. Choi
Filed: March 29, 2004	Atty. Dkt.: 7569/80993
For: **Improved Treatment of Migraine Headache**	

Comments in Response to Protest

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

On August 20, 2004, a Protest Under 37 CFR § 1.291(a) was filed against the above-captioned reissue application. Applicants have carefully reviewed the arguments made in the Protest and all of the references cited therein. As a result, they have the following comments for consideration by the Examiner.

A. Comments Relevant to § 112 Allegations

The Protest alleges that claims 6, 7 and 9 in the application are indefinite because it is unclear how a unit dosage form can be "coordinated." In particular, it is alleged that it is unclear how to sequentially administer two drugs when they are together in a single dosage form. The Protestor cites, in particular, the definition of coordinated in column 8, lines 50-51. This definition actually continues on to line 61 and reads as follows:

> "Coordinated" in the practice of the present invention refers to the sequential administration of metoclopramide and at least one drug, preferably an NSAID, wherein the metoclopramide is available in an effective concentration at the gastrointestinal tract of the subject within 1 to 30 minutes after administration (preferably in 5 minutes or less and, more preferably, in 3 minutes or less). At least one analgesic should be initially available at a therapeutically effective level in 5 to 60 minutes after administration. The therapeutically effective level of the analgesic should not be attained until after metoclopramide is present at an effective local gastrointestinal concentration.

In response, Applicants would like to initially point out that both the present application and its parent successfully went through prosecution without either of the Examiners in those cases finding reference to "coordinated unit dosage forms" to be either confusing or indefinite. In making the present allegation, the Protestor has taken terms out of context. The definition of "coordinated" was originally broad enough to encompass two sequentially taken tablets[1] as well as a single tablet in which analgesic does not become available for absorption into a patient's blood until after metoclopramide has been released and reached an effective concentration. However, as should be clear from a full reading of the application, when the term "coordinated" is combined with "dosage form" or "unit dosage form," it is referring to the controlled, sequential "delivery" or "release" of drugs.[2] In fact, these exact terms are used in the application when referring to coordinated dosage forms or unit dosage forms. For example, see:

Col 2, lines 22-24:

> Specifically, improved absorption of drug has been accomplished using "coordinated" dosage forms in which metoclopramide and NSAID are sequentially delivered.

Col. 3, line 64 – col. 4, line 6:

> In addition, the invention encompasses methods of increasing the rate of absorption of a drug into the bloodstream of a patient by administering it together with metoclopramide in a coordinated dosage form. As described above, the metoclopramide should be released first in an amount effective to increase gastric motility. A therapeutically effective amount of the drug should then be released and reach the gastrointestinal tract of the patient during the period that metoclopramide is having its effect.

Col. 4, line 65 - col. 5, line 6:

> A dosage form may also provide for coordinated delivery, i.e., delivery in which there is the sequential release of metoclopramide followed by analgesic. Again, methods for producing this type of dosage form are described below. Coordinated

[1] The sequential administration of two tablets, however, is not part of the presently pending claims.

[2] The definition in column 8 is, of course, still relevant. In other words, metoclopramide must still be available in an effective concentration in the gastrointestinal tract within 1 to 30 minutes, etc. However, in the context of a unit dosage form, the word "administration" is essentially synonymous with "delivery" or "release." When the full application is considered, Applicants do not believe that this is confusing.

dosage forms in which metoclopramide is used to promote drug absorption from the GI tract may also be used to administer agents other than analgesics and will be particularly useful for treating diseases or conditions associated with gastric stasis.

B. Comments Regarding Allegations Based on Prior Art Citations

All of the pending claims require either the presence of a coordinated unit dosage form (composition claims 6-13, 22-29 and 35; method claims 14-21) or acid-base storage stabilization (claims 5, 34 and 35).[3] For the reasons below, Applicants do not believe that the references cited in the Protest suggest either of these limitations.

Acid-Base Storage Stabilization

In considering claims directed to acid-base storage stabilized pharmaceutical compositions, it is important to remember that some incentive must have existed in the prior art to use dosage forms of this type for the combination of drugs recited in the present claims. Applicants have never suggested that the technology needed to make such dosage forms did not exist in the prior art. Instead, Applicants have argued that there was no motivation to apply such technology to dosage forms containing metoclopramide and an analgesic because it had not been previously recognized that degradation of active agents was a problem when these drugs are combined.

The main reference relied upon in the Protest in arguing that acid-base storage stabilized dosage forms were obvious is Gergely (U.S. 5,415,870). This describes effervescent tablets which contain: a) a solid edible organic acid; b) a component that forms a gas by reacting with the organic acid; and c) a salt formed as a result of the interaction. The edible organic acid is coated with the salt to prevent it from interacting to form a gas during storage. The reference never mentions metoclopramide or naproxen and does not suggest that acid-base storage stabilized forms, as this term is used in the application, should generally be preferred for analgesics.

[3] Claims 36-41 are dependent on either claim 34 or claim 35 and include their respective limitations.

The Protest suggests that the reference contains a generalized description of acids that includes analgesics such as naproxen and a method of preventing these acids from interacting with a base such as metoclopramide. However, this is a mischaracterization. The edible organic acids described in the reference are not the active agents in drug formulations, but rather the organic acids that are commonly ingested in foods, *e.g.*, citric acid, malic acid, tartaric acid, adipic acid or fumaric acid. There is no basis for concluding that the term "edible organic acids" as used in Gergely is intended to include drugs like naproxen. Applicants can also see no reasonable basis for thinking that one of skill in the art would refer to an analgesic or similar drug as an edible organic acid.[4] There is also no reason to conclude that the basic compounds described in the reference would include metoclopramide. Metoclopramide is clearly not a gas forming base, such as sodium carbonate or sodium bicarbonate (both of which are exemplified in the reference).

It is also important to note that acid-base storage stabilization as defined in the application requires a composition containing metoclopramide and an analgesic in which the potency of either of these active ingredients is not reduced by more than about 15% in 21 days storage at ambient temperature (15-20°C), or by more than about 5% in 14 days. The Protest appears to suggest that Gergely teaches that less than 15% of drug activity will be lost in the drug formulations disclosed therein. To support this view, the Protest refers to a portion of the reference that appears in col. 4, line 61 - col. 5, line 1. This reads as follows:

> In the preparation of the effervescent base, a reaction loss of 5 to 10%, but not more than 15%, may be expected, the resulting CO_2 and water being removed by means of a vacuum. This reaction loss of 5 or 10% of the total amount of citric acid, bicarbonate and carbonate used means that, at a reaction loss of 5%, 16.8% and, at a reaction loss of 10%, 33.5% of the total amount of effervescent components used are present as monocitrate. In fact, this would in general lead to slowly dissolving effervescent tablets, since the sodium salt formed as a result acts as a buffer system and slows down the dissolution, but not when, according to the invention, foreign acids have been incorporated.

It appears to Applicants that the passage quoted above is not referring to the loss of activity of an active drug agent, but rather to a loss of effervescent components. This is obviously

[4] In fact, referring to naproxen or other analgesics as "edible organic acids" strikes Applicants as being bizarre. This is simply not terminology normally used in connection with these drugs.

not storage stabilization as defined in the reissue application. Even if one were to accept that effervescence was a legitimate drug activity (and this is not suggested by the reference itself), the time frame for activity losses required by the reissue application is not provided in the reference. Thus, it is not clear that the percentages referred to in the reference include a loss of activity over 21 days at ambient temperature or how they would relate to a loss of not more than 5% in 14 days.

For the reasons provided above, Applicants believe that the main reference that has been cited in the Protest in attempting to establish the obviousness of acid-base storage stabilized pharmaceutical compositions really does not suggest the use of these compositions at all. In rejecting claim 34, the Protest also relies on a reference by Seiyaku (EP 823 255). However, this European patent application was not published until November of 1998, and it would therefore not constitute prior art with respect to the priority applications that Applicants filed on November 10, 1997 and November 12, 1996.

Coordinated Dosage Forms

There are two main references that are relied upon by the Protest in rejecting claims involving coordinated dosage forms. The first of these is Moore, *et al.* (*Am. Fam. Physician 56*:2039-2048 (1997)). This reference was published on November 15, 1997. Thus, it would not be prior art with respect to priority application 08/966,506, filed November 10, 1997 or with respect to 08/748,332, filed on November 12, 1996. A review of these applications should make it clear that they fully disclose coordinated dosage forms and define them in the same manner as the reissue application.[5] For the convenience of the Examiner, Appendix A is attached that presents the presently pending claims and points to specific sections of one of Applicants' priority applications, the '506 application, to show how it supports these claims. Based upon this, Applicants submit that the priority application provides express literal support for all of the elements in the presently pending claims except for dependent claims in which: a) the number

[5] Appendix A points to various portions of the November 10, application that provide support for the present claims. This application was selected because it issued as U.S. 6,077, 539 and the Examiner can therefore readily check the accuracy of Applicants' statements. In order to facilitate comparison, the Appendix cites passages in the issued patent. These are, of course, in the application as well and Applicants will be happy to provide exact cross references if the Examiner would like.

of specific individual NSAIDs recited has been increased; and b) there is the inclusion of NSAIDs "formulated to be long acting." However, it is not required that an element be recited verbatim for it to be supported by a patent specification and these basic concepts are both clearly supported by the earlier filed application. Specifically, the priority application includes NSAIDs as a class. In fact, the claims that issued in the priority application encompass either all long acting NSAIDs (issued claim 1) or simply all NSAIDs (claim 2). Thus, the inclusion of additional NSAIDs to the many already expressly recited in the priority application allows for the addition of new dependent claims but does not broaden the scope of the claims supported by the original application. With respect to NSAIDs "formulated to be long acting," the priority application does clearly disclose "long acting NSAIDs" and, from a practical biological point of view, an NSAID formulated to be long acting is just a form of long acting NSAID. Again, Applicants submit that, conceptually, the full scope of the pending claims is supported by the priority application. Finally, Applicants would like to point out that the neither of the elements added as dependent claims in the reissue application are disclosed in the reference cited.

Since Moore is a critical reference with regard to all of the arguments made concerning coordinated dosage forms, its failure to constitute prior art is a serious defect and this alone should be sufficient to obviate the allegations that have been made. Beyond this, the reference by Moore is concerned with the sequential administration of separate drug entities. This may be contrasted with Applicants' claims which are concerned with the timing of release of active agents from a single unit dosage form.

The second reference that is relied upon in the Protest in combination with Moore is Greiff (*Clin. Pharmacokinetics 27*:447-461 (1994)). This teaches that when metoclopramide and paracetamol are given together, the Tmax plasma concentration for paracetamol is reduced from about 37.5 minutes to about 22.5 minutes. This measurement is specific to paracetamol and is concerned with how rapidly it is absorbed when delivered at the same time as metoclopramide. In contrast, as discussed above, coordinated delivery as used in the reissue application is concerned with the timing of drug release, *i.e.*, when the drugs become *available* for absorption across the GI tract. This is reflected in the definition provided in col. 8, lines 50-61:

> F. "Coordinated" in the practice of the present invention refers to the sequential administration of metoclopramide and at least one drug, preferably an NSAID, wherein the metoclopramide is available in an effective concentration at the gastrointestinal tract of the subject within 1 to 30 minutes after administration (preferably in 5 minutes or less and, more preferably, in 3 minutes or less). At least one analgesic should be initially available at a therapeutically effective level in 5 to 60 minutes after administration. The therapeutically effective level of the analgesic should not be attained until after metoclopramide is present at an effective local gastrointestinal concentration.

It should be apparent from the above quotation that coordinated delivery is primarily concerned with the timing of drug release and not directly with drug absorption across the GI tract. The overall rate of absorption *as measured from the time of drug ingestion* should be reduced by coordinated delivery (this is pointed out both in the specification and claims of the reissue application), but the reason for this is due to the release characteristics of the dosage form. Claims specifying coordinated unit dosage forms, according to the definition above, require that the analgesic become *available* in the GI tract at a therapeutically effective level in 5-60 minutes after administration and only after metoclopramide has reached a concentration where it is stimulating motility. Thus, if metoclopramide was released at a rate such that an effective concentration was attained in 10 minutes after ingestion, a therapeutically effective dose of analgesic should not be released into the GI tract until after this time.

It appears that the Protestor has interpreted the last two sentences of the definition of "coordinated" provided above as requiring that analgesic be present *in the plasma* of a patient at 5-60 minutes after administration and that a therapeutically effective level of NSAID be present *in a patients' plasma* only after an effective level of metoclopramide is present in the GI tract. However, when read in context with the rest of the definition, Applicants believe that it should be apparent that what is actually being referred to is the availability of a therapeutically effective dose of NSAID released *in the GI tract*. This view is also supported elsewhere in the specification. For example, col. 3, line 64 - col. 4, line 5 read as follows:

> In addition, the invention encompasses methods of increasing the rate of absorption of a drug into the bloodstream of a patient by administering it together with metoclopramide in a coordinated dosage form. As described above, the metoclopramide should be released first in an amount effective to

> increase gastric motility. A therapeutically effective amount of the drug should then be released and reach the gastrointestinal tract of the patient during the period that metoclopramide is having its effect. For the purposes of the invention absorption is defined as the time from which the drug is administered until the time that it reaches a peak plasma concentration.[6]

The rate at which paracetamol is absorbed once in the GI tract (*i.e.*, the teaching of Greiff) has no direct relevance to coordinated delivery as defined in the reissue application. There is also no reason why release of analgesic from Applicants' claimed compositions should be delayed until 20 minutes after a tablet is ingested as the Protestor appears to suggest is taught in the references. Instead, in a coordinated dosage form, release of analgesic depends upon the timing and rate of release of metoclopramide. It occurs only after gastric motility has been increased, regardless of whether the increase in motility happens 5 minutes after ingestion or 20 minutes after ingestion.

Overall, Applicants submit that the two primary references relied upon by the Protest in arguments concerning coordinated dosage forms are irrelevant - Moore because it is not prior art and Grief because it is concerned with a characteristic that is not directly material to the inventions claimed. One additional reference used by the Protestor in arguments concerning claims 13, 19, 25 and 41 (Chen U.S. 6,106,862, filed August 13, 1998) does not appear to constitute prior art to the reissue application.

Conclusion

In light of the discussion above, Applicants respectfully submit that the arguments that have been put forward in the Protest filed on August 20, 2004 are insufficient to reject the claims that are presently pending in the above-captioned application. Moreover, Applicants submit that a review of the references that have already been cited in connection with this case indicates that nothing new of any significance has been added by the references cited in the Protest. It is therefore respectfully requested that the claims presently pending in the application and which originally issued in US 6,479,551 be allowed once again.

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[6] Note that time for absorption using the definition provided in the application will be affected by drug release. Absorption as described in Greiff appears to be only concerned with the time necessary for drug to enter the plasma *after* it has already been made available in the gastrointestinal tract.

If, in the opinion of the Examiner, a phone call may help to expedite the prosecution of this application, the Examiner is invited to call Applicants' undersigned attorney at (202) 419-7013.

Respectfully submitted,

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